## REMARKS

All formality issues raised in the Office Action are overcome by the amendments to the form of the claims.

The only issue that is not addressed by the amendments is raised in point viii) of the Office Action, under section 112, second paragraph, where it is alleged that it is unclear who the subject is that needs prevention of infection and how one can say whether the infection is prevented.

The prevention of infections per se, e.g., of tuberculosis (see, for example, claim 12), or of mycobacterial infections (see, for example, claim 10) or of other bacterial infections (see, for example, claims 14 and 15), are common in the pharmaceutical arts.

As support, attached is a printout of a table titled "Drugs Given to Prevent Infections" printed in the Blood & Marrow Transplant Newsletter, Issue # 19, Vol. 4, No. 5, September 1993, authored by G. Yee and D. L. Stanley. The table extends through six pages and identifies compounds by generic and trade names and groups them into various classes, e.g., antibiotics, antifungals, antivirals, etc.

Also attached are two abstracts, i.e., Ji B. et al., Effectiveness of rifampin, rifabutin, and rifapentine for preventive therapy of tuberculosis in mice, Am Rev Respir Dis. 1993 Dec;148(6 Pt 1):1541–1546 and Chapuis, L. et al., Preventive therapy of tuberculosis with rifapentine in immunocompetent and nude mice, Am. J. Respir. Crit. Care Med. 150:1355-1362.

All of these references clearly demonstrate that the prevention of infections per se of various types, including of tuberculosis, which is caused by a certain type of mycobacteria, has been known by those of ordinary skill in the art for a long time prior to the filing date of the present application. Thus, one of ordinary skill in the art would know the scope of what is claimed; and thus, the indefiniteness rejections are not warranted.

One of ordinary skill in the art, for example, would know that prevention of infections is desirable at most times by most people, and especially in certain settings and on subjects at high risk, e.g., healthcare workers or caregivers exposed to various infectious agents, to persons with depressed immune systems, e.g., HIV patients often develop tuberculosis, high risk populations who may be or have been exposed to tuberculosis or various respiratory bacterial infections (for example, in the case of an outbreak), burn victims, persons undergoing operations, immunosuppressed persons with a history of exposure and those with

evidence of serum conversion (tuberculosis antigens are found, although the disease is not yet broken out), etc. Prevention of infections can be and has been practiced by those of ordinary skill in the art using other agents. This alone rebuts the Examiner's concerns.

Additionally, applicants teach that the "compounds of the invention have a higher anti-mycobacterial activity than known tuberculosis agents, especially rifampicine, " and that "they additionally show anti-microbial activity against ordinary bacteria." See page 2, lines 3-5. These teachings are confirmed by data presented in the specification. See examples 6 and 7, and the results thereof in tables 1 and 2.

Reconsideration is respectfully requested.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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Am Rev Respir Dis. 1993 Dec;148(6 Pt 1):1541-6. Related Articles, Links

# Effectiveness of rifampin, rifabutin, and rifapentine for preventive therapy of tuberculosis in mice.

Ji B, Truffot-Pernot C, Lacroix C, Raviglione MC, O'Brien RJ, Olliaro P, Roscigno G, Grosset J.

Faculte de Medecine Pitie-Salpetriere, Paris, France.

To identify alternative regimens for preventive therapy of tuberculosis, the pharmacokinetics and antimicrobial activities of rifampin (RMP), rifabutin (RBT), and rifapentine (RPT) were compared in BCG-vaccinated and M. tuberculosis-infected immunocompetent mice. RPT showed the highest serum peak level (Cmax) and the longest half-life (t1/2), whereas RBT displayed the lowest Cmax and the shortest t1/2. On weight-to-weight basis, both RPT and RBT were more bactericidal than RMP. The activity of RMP was significantly reduced when the frequency of administration was reduced from six to three times weekly, whereas significant bactericidal activity was still observed in mice treated with RPT, 10 mg/kg up to once fortnightly, or RBT, 10 mg/kg twice weekly. Because the bactericidal activity of RBT, 10 mg/kg six times/wk for 6 wk, or RPT, 10 mg/kg two times/wk for 12 wk, was comparable to that of RMP, 10 mg/kg six times/wk for 12 wk in mice, the two regimens are appropriate for clinical trials of preventive therapy of tuberculosis.

Am. J. Respir. Crit. Care Med., Vol 150, No. 5, Nov 1994, 1355-1362.

# Preventive therapy of tuberculosis with rifapentine in immunocompetent and nude mice

**L Chapuis, B Ji, C Truffot-Pernot, RJ O'Brien, MC Raviglione and JH Grosset**
Faculte de Medecine, Pitie-Salpetriere, Paris, France.

The effectiveness of intermittent administration of rifapentine (RPT), with or without isoniazid (INH), for preventive therapy of tuberculosis was evaluated in immunocompetent (normal) and nude mice. After infection with a small inoculum of Mycobacterium tuberculosis H37Rv, normal mice developed a chronic and nonfatal infection, and the bacterial population became relatively stable after an initial period of limited multiplication. On the other hand, nude mice developed an acute and fatal infection, and all untreated mice died within 5 wk, with very high colony-forming-unit (CFU) counts in their organs. Various degrees of bactericidal activity were shown in normal mice after daily treatment with rifampin (RMP) plus pyrazinamide (PZA) for 13 wk, INH daily for 26 wk, or RPT once weekly for 13 or 26 wk or once fortnightly for 26 wk. The activity of RPT was significantly enhanced when INH was added at the same dosing frequency. In nude mice the response of M. tuberculosis infection to certain regimens was less favorable than that in normal mice, suggesting that preventive therapy may be less effective in severely immunodeficient hosts even during treatment. After chemotherapy was stopped, virtually all nude mice relapsed within 12 wk regardless of the regimen administered, whereas no or very few relapses were observed in normal mice that had been treated with RMP+PZA daily for 13 wk, or RPT alone or RPT+INH once weekly for 26 wk. The latter three regimens and RPT+INH once weekly for 13 wk may be applied for fixed-duration preventive therapy in human immunodeficiency virus (HIV)-negative subjects. (ABSTRACT TRUNCATED AT 250 WORDS)

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# Drugs Given to Prevent Infections

*By Gary Yee Pharm D and Denise L Stanley Pharm D.*

| Generic Name | Trade Name | Route Given | Common Side Effects |
|---|---|---|---|
| **Antibiotics** | | | |
| Amikacin | Amikin | IV or oral | Diarrhea, change in kidney function or hearing.1 |
| Ampicillin/clavulanic acid | Augmentin | oral tablet<br>oral liquid | N/V/D, GI upset, rash, change in liver function. |
| Aztreonam | Azactam | IV or oral | Allergic reactions, rash, N/V/D, change in liver function. |
| Cefoperazone | Cefobid | IV | Allergic reactions, rash, N/V/D, bleeding problems, vein irritation. |
| Cefotaxime | Claforan | IV | As above, except for bleeding problems. |
| Ceftazidime | Fortaz, Tazidime | IV | As above, and change in kidney function. |
| Ciprofloxacin | Cipro | oral tablet, IV | GI upset, N/V/D, headache, change in kidney or |

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| | | | liver function. Caution in age < 18. Drug interactions. |
| Colistin Sulfate or Polymixin E | Colymycin S | oral liquid | N/V/D, GI upset. |
| Gentamicin | Garamycin | IV or oral | Diarrhea, change in kidney function(1) or hearing (1), muscle weakness. (1) |
| Imipenem/cilastatin | Primaxin | IV | Allergic reactions, rash, vein atation, N/V/D, seizures, change in kidney function. |
| Metronidazole | Flagyl | oral tablet, IV | N/V/D, GI upset, metallic taste, change in liver function. Avoid alcohol. Discolors urine. |
| Mezlocillin | Mezlin | IV | Allergic reactions, rash, N/V/D, bleeding problems or decreased blood counts, change in kidney or liver function. |
| Neomycin | Mycifradin | oral tablet | GI upset N/V/D, rash, change in kidney function. (1) |

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| Norfloxacin | Noroxin | oral tablet | Headache, dizziness, nausea, change in liver or kidney function. Caution in age < 18. |
| Ofloxacin | Floxin | oral tablet, IV | GI upset, diarrhea, insomnia, headache, dizziness. Caution in age < 18. |
| Penicia V K+ | Veetids<br>Pen Vee K | oral tablet<br>oral liquid/IV | Skin rash, GI upset, diarrhea, fever. |
| Piperacillin | Pipracil | IV | Same as above, under mezlocillin. |
| Polymixin B | Aerosporin | oral liquid | N/V/D or GI upset. |
| Rifampin | Rifadin, Rimactane | oral capsule | Reddish discoloration in urine, stool, tears, sweat; N/V, flu-like symptoms, rash, change in liver function. Drug interactions. |
| Ticarcillin or Ticarcillin/clavulinate | Ticar<br>Timentin | IV | Sanie as above, under mezlocillin. |
| Tobramycin | Nebcin | IV or oral | Same as above, under mezlocillin. |
| Trimethoprim/ Sulfamethoxazole or TMP/SMX | Bactrim,<br>Bactrim DS<br>Septra | oral tablet or IV | N/V/D, GI upset, rash, decreased blood counts, change in kidney or liver |

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| | | | function. |
| Vancomycin | Vancoled<br><br>Vancocin | oral capsule, oral liquid, IV | Allergic reactions, rash, vein irritation, change in kidney function or hearing, decreased white blood cell count, stomach upset. |
| **Antifungals** | | | |
| Amphotericin B | Fungizone | liquid, IV, nasal spray, mouthrinse | N/V/D, metallic taste, change in kidney function, change in electrolytes, rash, fever, severe allergic reactions, anemia. |
| Clotrimazole | Mycelex | oral troches | N/V, change in taste, change in liver function. (1) |
| Fluconazole | Diflucan | oral tablet, IV | N/V/D, rash, change in liver function, drug interactions. |
| Itraconazole | Sporonox | oral capsule | N/V/D, change in liver function, drug interactions. |
| Ketoconazole | Nizoral | oral tablet | N/V/D, headache, dizziness, rash, change in liver function, food and |

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| | | | drug interactions. |
| Nystatin | Nilstat, Mycostatin | oral liquid | GI upset, N/V/D, change in taste. |
| **Antivirals** | | | |
| Acyclovir | Zovirax | oral capsule, oral liquid/IV | Diarrhea, dizziness, rash, fatigue, change in kidney function, vein irritation, confusion, change in liver function. |
| Ganciclovir/DHPG | Cytovene | IV | Decreased white blood cells, anea fever, rash, change in liver function. |
| Foscarnet | Foscavir | IV | Headache, fatigue, nausea, fever, change in kidney function, change in electrolytes. |
| **Antiprotozoals** | | | |
| Pentamidine | Pentam | Inhalation or IV | Decreased blood pressure, rash, N/V, decreased blood counts, change in kidney or liver function. |
| Trimethoprim/ Sulfamethoxazole or TMP/SMX | Bactrim, Septra, | oral tablet or IV | Same as above, under antibiotics. |

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| | Septra DS | | |
| **Tropical/Other** | | | |
| Chlorhexidine | Peridex | oral rinse | Metallic taste, N/V, staining of teeth, minor oral irritation, allergic reactions. (1) |
| IVIG | Sandoglobulin<br>Gammagard<br>PolyGam<br>Cytogam | IV | Fever, chills, allergic reactions, rash. |
| **Abbreviations:** | | | |
| N=nausea, | V = vomiting | D = diarrhea | |
| 1= not commonly seen at the dose used for prophylaxis | 2= affected by multiple foods; should he taken with orange juice or other acidic foods | | |

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*Someone You Should Know*